# Sex-Related Location of Head and Neck Melanoma Strongly Argues for a Major Role of Sun Exposure in Cars and Photoprotection by Hair

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Head and neck melanomas (HNMs) are frequent and have a poorer prognosis than melanomas at other sites. Photoprotection in these locations is difficult. In this population-based study of 279 HNMs diagnosed in a French region between 2004 and 2009, major differences were found between genders. A clearcut, sex-related distribution was found between a "peripheral" area (scalp, forehead, temples, ears, and neck) and a "central" one (other parts of the face), with 56.7% of HNMs being located in the peripheral area in men and 79.3% in the central area in women ($P<0.0001$). Moreover, HNMs located in the peripheral area occurred on the left side in 57.6% of men and on the right side in 73.1% of women ($P=0.009$). Peripheral HNMs differed from central HNMs by a higher proportion of invasive tumors, nodular or superficial spreading melanomas, and a lower proportion of lentigo maligna melanomas (LMMs). We hypothesized that this differential distribution between men and women could be explained mostly by a major role of long-term photoprotection by hair and sun exposure in a car. Important public health messages could result from these observations, such as the role of hairstyles in melanoma prevention and the importance of reducing sun exposure in a car, particularly in professional drivers.

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## INTRODUCTION

The worldwide incidence of cutaneous melanoma (CM) has been increasing for at least 30 years in western populations, with some estimates showing a doubling of the number of cases over the past two decades (Gray-Schopfer *et al.*, 2007). CM is a heterogeneous group of tumors with broad biological variability depending on different factors, including anatomic location (Gillgren *et al.*, 2000; Durbec *et al.*, 2012). Among specific anatomic locations, the head and neck area is of particular interest for several reasons. First, it is exposed to the highest level of UV radiation, including both chronic and intermittent sun exposure. Second, this region accounts for 9% of the total body surface (Gillgren *et al.*, 1999), but between 12 and 20% of all CMs (Garbe *et al.*, 1995; Gillgren *et al.*, 1999, 2000; Lachiewicz *et al.*, 2008; Barbe *et al.*, 2011). In France, the relative frequency of head and neck melanomas (HNMs) has been estimated at 22 and 19.5% of all invasive CMs in two population-based studies (Lipsker *et al.*, 2007; Barbe *et al.*, 2011) and at 59% of *in situ* CMs in one study (Barbe *et al.*, 2011). Finally, numerous studies have demonstrated that HNMs have a poorer prognosis than CMs at other sites (Urist *et al.*, 1984; Weinstock *et al.*, 1988; Thörn *et al.*, 1989; Law and Wong, 1994; Levi *et al.*, 1998; Kienstra and Padhya, 2005; Golger *et al.*, 2007; Lachiewicz *et al.*, 2008; Tseng and Martinez, 2011). In a recent population-based study using the SEER (Surveillance, Epidemiology, and End Results) program, the location on the scalp and neck was an independent adverse prognostic factor of disease-specific survival in a multivariate analysis taking into account age, sex, ulceration, and Breslow thickness (Lachiewicz *et al.*, 2008).

In view of their frequency, their severity, and their epidemiological characteristics, HNMs require further study regarding their etiological factors to achieve more efficient and specific prevention. Among different approaches, the study of the topographical distribution within this area seems relevant in clarifying the pathogenesis of HNM. Differences in CM location between men and women are well known for the whole body surface, with a classical predominance on the trunk in men and on the lower extremities in women. In recent studies, a reduction in these differences was observed and attributed to changes in clothing habits (Clark *et al.*, 2007).

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*Abbreviations: CM, cutaneous melanoma; HNM, head and neck melanoma; LMM, lentigo maligna melanoma; SEER, Surveillance, Epidemiology and End Results*

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In contrast with these global data, very few studies have analyzed the precise location of CM within the head and neck area and compared anatomic distribution of HNM between men and women (Ringborg *et al.*, 1993; Gillgren *et al.*, 1999, 2000). In our clinical practice, we had the impression that there was a sex-dependent distribution in this area. This prompted us to test this hypothesis in a population-based study, using the French regional melanoma registry OMECHA (Observatoire des Mélanomes de la Région Champagne-Ardenne).

## RESULTS

Between 2004 and 2009, 279 HNMs were diagnosed in the Champagne-Ardenne region, representing 25.8% of all incident CMs during this period. These 279 cases included 128 *in situ* CMs (i.e., 54.2% of all *in situ* CMs in the study period) and 151 invasive CMs (i.e., 17.9% of all invasive cases). The world-standardized incidence rate of HNM was estimated at 1.62/100,000 inhabitants/year for both sexes: 1.67/100,000 in men and 1.59/100,000 in women. Comparison between men and women for clinical and histological characteristics of *in situ* and invasive CMs did not show any differences concerning age, histological subtype, Breslow thickness, and ulceration (Table 1). In contrast, anatomic distribution differed greatly according to gender ($P<0.0001$, Table 2). Although location on the cheek was the most frequent in both sexes ($n=132$, 48% (42.1–53.9)), its proportion clearly differed between sexes (63.2% (55.6–70.8) in women vs. 28.3% (20.3–36.4) in men, $P<0.0001$). Other frequent locations in men were the ears ($n=22$, 18.3%), the temple ($n=19$, 15.8%), and the neck ($n=12$, 10%), whereas no frequent location apart from the cheek was observed in women.

Further analysis of this topographical distribution made it possible to distinguish two areas within the head and neck zone where the differences between sexes were the most marked: a ''peripheral'' area comprising the scalp, forehead, temple, ears, and neck, and a ''central'' area comprising the eyelids, nose, cheeks, and area around the mouth/chin (Figure 1). In men, HNMs were located in the peripheral area in 56.7% (47.8–65.5) of cases, whereas 79.3% (73.0–85.7) of cases diagnosed in women occurred in the central area ($P<0.0001$; Table 3). Accordingly, 68% (58.9–77.1) of peripheral HNMs occurred in men, whereas 70.3% (63.5–77.1) of central HNMs occurred in women ($P<0.0001$). The proportions of cases in each gender, as compared with the total number of cases by subsite, are illustrated in Figure 2. These differences according to gender remained significant when *in situ* and invasive HNMs were considered separately. Some 36% (22.7–49.3) of *in situ* CMs were located in the peripheral area in men versus 16% (7.7–24.3) in women ($P=0.01$). Differences were even more significant for invasive HNMs, with 71.4% (60.8–82.0) of cases being located in the peripheral area in men versus 25% (15.5–34.5) in women ($P<0.0001$).

We further compared the location of HNMs between men and women taking laterality into account. For this analysis, cases located on the midline of the head and neck area were excluded. When both peripheral and central areas were considered, no significant difference regarding the side was observed between genders, with 56.6% (47.2–66.0) of cases on the left side in men and 51.1% (42.7–59.5) on the right side in women ($P=0.23$). When only HNMs located on the peripheral area were taken into account (Table 4), a highly differential anatomic distribution was observed according to sex, with 57.6% (45.0–70.2) of cases located on the left side in men versus 73.1% (56.0–90.1) on the right side in women ($P=0.009$).

**Table 1. Clinical and histological characteristics of head and neck melanomas in the whole population and according to gender**

| | All cases[1] | Men[1] | Women[1] | *P*-value |
|---|---|---|---|---|
| *All cases* | $n=279$ | $n=121$ | $n=158$ | |
| Age, y | | | | 0.10 |
| Mean ± SD | 71.5 ± 13.8 | 70.5 ± 13.3 | 73.2 ± 14.1 | |
| Median (range) | 74 (17–99) | 72.2(23–99) | 75.5 (18–97) | |
| *In situ melanomas* | $n=128$ (45.9) | $n=51$ (39.8) | $n=77$ (60.2) | 0.19 |
| Age, y | | | | 0.28 |
| Mean ± SD | 72 ± 10.5 | 71.3 ± 10.4 | 73.3 ± 10.5 | |
| Median (range) | 73 (38–93) | 72.1(38–89) | 75.1 (40–94) | |
| Histological type | | | | 0.16 |
| SSM | 5 (3.9) | 0 (0) | 5 (6.5) | |
| LMM | 123 (96.1) | 51 (100) | 72 (93.5) | |
| *Invasive melanomas* | $n=151$ (54.1) | $n=70$ (46.4) | $n=81$ (53.6) | 0.82 |
| Age, y | | | | 0.21 |
| Mean ± SD | 71.1 ± 16.1 | 69.8 ± 15.2 | 73.1 ± 16.8 | |
| Median (range) | 74 (17–99) | 72.4 (23–100) | 77.9 (18–97) | |
| Histological type | | | | 0.67 |
| SSM | 38 (25.3) | 19 (27.1) | 19 (23.8) | |
| NM | 31 (20.7) | 16 (22.9) | 15 (18.8) | |
| LMM | 72 (48) | 30 (42.9) | 42 (52.5) | |
| Unclassifiable | 5 (3.3) | 3 (4.3) | 2 (2.5) | |
| Unspecified | 4 (2.7) | 2 (2.9) | 2 (2.5) | |
| Breslow thickness, mm | | | | 0.98 |
| Mean | 2.20 | 2.00 | 2.40 | |
| Median (range) | 1.30 (0.02–15) | 1.40 (0.15–12) | 1.15 (0.02–15) | |
| Ulceration | | | | 0.48 |
| Yes | 37 (24.8) | 19 (27.5) | 18 (22.5) | |
| No | 112 (75.2) | 50 (72.5) | 62 (77.5) | |

Abbreviations: LMM, lentigo maligna melanoma; NM, nodular melanoma; SSM, superficial spreading melanoma; y, years.
[1]Data are expressed as *n* (%) unless otherwise indicated.

**Table 2. Descriptive topographic analysis of HNM location according to sex**

| | *In situ* melanomas | | | Invasive melanomas | | | *In situ* and invasive melanomas | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Location | M[1] | W[1] | Total[1] | M[1] | W[1] | Total[1] | M[1] | W[1] | Total[1] | *P*-value |
| Scalp | 1 (2) | 0 (0) | 1 (0.8) | 7 (10) | 2 (2.5) | 9 (6) | 8 (6.7) | 2 (1.3) | 10 (3.6) | |
| Forehead | 4 (8) | 2 (2.7) | 6 (4.8) | 3 (4.3) | 4 (5) | 7 (4.7) | 7 (5.8) | 6 (3.9) | 13 (4.7) | |
| Temple | 5 (10) | 6 (8) | 11 (8.8) | 14 (20) | 3 (3.7) | 17 (11.3) | 19 (15.8) | 9 (5.8) | 28 (10.2) | |
| Eyelid | 5 (10) | 2 (2.7) | 7 (5.6) | 2 (2.8) | 10 (12.5) | 12 (8) | 7 (5.8) | 12 (7.7) | 19 (6.9) | |
| Ear | 6 (12) | 3 (4) | 9 (7.2) | 16 (22.8) | 5 (6.2) | 21 (14) | 22 (18.3) | 8 (5.2) | 30 (10.9) | <0.0001 |
| Nose | 6 (12) | 2 (2.7) | 8 (6.4) | 3 (4.3) | 5 (6.2) | 8 (5.3) | 9 (7.5) | 7 (4.5) | 16 (5.8) | |
| Cheek | 20 (40) | 54 (72) | 74 (59.2) | 14 (20) | 44 (55) | 58 (38.7) | 34 (28.3) | 98 (63.2) | 132 (48) | |
| Area around the mouth/chin | 1 (2) | 5 (6.7) | 6 (4.8) | 1 (1.4) | 1 (1.3) | 2 (1.3) | 2 (1.7) | 6 (3.9) | 8 (2.9) | |
| Neck | 2 (4) | 1 (1.3) | 3 (2.4) | 10 (14.3) | 6 (7.5) | 16 (10.7) | 12 (10) | 7 (4.5) | 19 (6.9) | |
| Total | 50 | 75 | 125 (100) | 70 | 80 | 150 (100) | 120 | 155 | 275[2] (100) | |

Abbreviations: HNM, head and neck melanoma; M, men; W, women.
[1]Data are expressed as *n* (%).
[2]Precise location within the head and neck was unknown in four cases (1.4%).


**Figure 1. Peripheral and central areas of the head and neck, as defined by the sex-related distribution of cutaneous melanomas.** Images are used with subjects' informed consent.

Apart from these sex-related differences, HNMs in the peripheral area differed from those in the central area by a younger age of occurrence (median: 70 vs. 75 years, $P<0.0001$), a lower ratio of *in situ*/invasive tumors (0.42 vs. 1.18; $P<0.0001$), a higher proportion of nodular melanomas

**Table 3. Distribution of head and neck melanomas (HNMs) according to sex and major topographic areas in the whole study population**

| | Men[1,2] (*n*=120) | Women[1,2] (*n*=155) | *P*-value |
|---|---|---|---|
| *Topographic area* | | | <0.0001 |
| Peripheral | 68 (56.7) | 32 (20.7) | |
| Central | 52 (43.3) | 123 (79.3) | |

[1]Data are expressed as *n* (%).
[2]Precise location within the head and neck was unknown in four cases (1.4%).

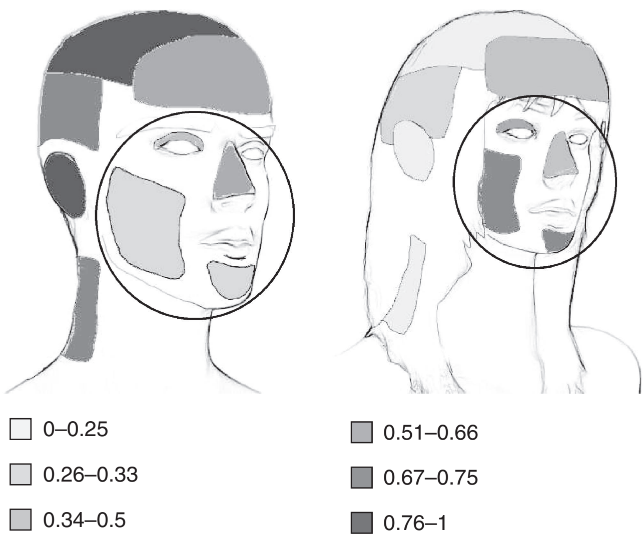


**Figure 2. Differential anatomic distribution of head and neck melanomas (HNMs) according to gender.** For each area, the proportion of cases in each sex among the total number of cases has been calculated and translated into corresponding levels of gray. The subjects in the photographs provided written and informed consent for publication.

**Table 4. Laterality of head and neck melanomas (HNMs) located in the "peripheral" area, according to sex**

| | Men[1,2] ($n=59$) | Women[1,2] ($n=26$) | *P*-value |
|---|---|---|---|
| *Side*[2] | | | 0.009 |
| Left | 34 (57.6) | 7 (26.9) | |
| Right | 25 (42.4) | 19 (73.1) | |

[1]Data are expressed as *n* (%).
[2]For the "peripheral" area of the head and neck, side was unknown in 10 cases (10%). Five cases (5%), which were located on the midline of the head and neck area, were excluded from this analysis.

(16.2% (8.9–23.4) vs. 8.8% (4.5–13.0), $P=0.06$) and superficial spreading melanomas (28.3% (19.4–37.2) vs. 8.8% (4.5–13.0), $P<0.001$), and a lower proportion of lentigo maligna melanomas (LMMs; 53.5% (43.7–63.4) vs. 80.7% (74.8–86.6), $P<0.001$).

In multivariate analysis, male gender (odds ratio (OR) = 5.4 (3.0–9.6), $P<0.0001$), older age of occurrence (OR = 1.006 (1.001–1.010), $P=0.01$), invasive tumors (OR = 1.9 (1.01–3.7), $P=0.046$), and nodular melanoma/superficial spreading melanoma histological types (OR = 2.8 (1.4–5.7), $P=0.004$) were significantly associated with the peripheral location of HNMs.

## DISCUSSION

To the best of our knowledge, this is a previously unreported population-based study investigating the precise location of HNMs in western Europe. We observed highly significant topographical differences between men and women. Nearly four out of five HNMs in women were located on a central area of the face comprising the eyelids, the nose, the cheeks, and the area around the mouth and chin. In contrast, 57% of HNMs occurring in men were located at the periphery of the head and the neck area, comprising the scalp, the forehead, the temples, the ears, and the neck. Moreover, when considering separately lesions located on this peripheral area in both genders, 73% occurred on the right side in women, whereas a large majority (57.6%) of those occurring in men were on the left side. These results may strongly argue for an important role of sun exposure in cars and photoprotection by hair in favoring and preventing, respectively, the occurrence of HNMs.

These results and hypotheses are limited by two main factors. They rely on a relatively small number of HNMs from a specific French region, and it remains uncertain whether they would be reproducible elsewhere. No individual data (such as hairstyle, alopecia, time spent in a car, or usual side when traveling in a car) were available to confirm major hypotheses likely to account for the observed sex-related distribution of HNMs.

The strengths of this study, in contrast, were its population-based design and the precise assessment of melanoma location, including laterality. Only few epidemiological, population-based studies concerning HNM are available. The largest study, to date, relied on the SEER program, in which scalp and neck were coded together as a single site, so that the authors were unable to examine more precise locations (Lachiewicz *et al.*, 2008). In a retrospective series of 581 patients, (Ringborg *et al.,* 1993) divided anatomic sites within the head and neck as follows: eyelid and corner of the eye, auricle and external ear canal, other parts of the face, and scalp and neck together. They found that tumors of "other parts of the face" were significantly more frequent in women. Conversely, CMs of the auricle and external ear canal, scalp, and neck were more common in men. However, this difference in distribution between genders was not discussed. The authors only put forward the role of the density of melanocytes and sun exposure to explain the high relative frequency of facial CM in both sexes, considering the small surface of this body area.

In our study, the most frequent location in both sexes was the cheek, which represents the major part of the skin surface of the face. This is in accordance with data from the Swedish National Cancer Registry, which showed that the "face" (without further precision) was the predominant site, including 71% of HNMs (Gillgren *et al.*, 1999, 2000). These authors also mentioned a differential anatomic distribution according to gender, both for *in situ* and invasive HNMs, the face location being more frequent in women, whereas CMs of the auricle, external ear canal, scalp, and neck were more frequent in men. This result, however, was not specifically discussed.

Our study confirms and extends these data by highlighting two clearcut, topographic patterns of HNMs: a central distribution characteristic of women and a peripheral one characteristic of men. Both *in situ* and invasive CMs followed this differential distribution, with differences being more pronounced for invasive cases. The main hypothesis to explain this sex-specific distribution could be a long-term sun-protective role of hair cover. Sun exposure is the major environmental cause of CM. In the early 1980s, Magnus (1981) provided striking evidence of the role of clothing and sun-exposure habits by analyzing CM incidence rates by tumor site from 1955 to 1977 in the Norwegian population. He found that CMs located on the trunk and lower extremities had increased much more than HNMs among younger generations, consistent with changes in clothing and sun-exposure habits. Although the role of sun protection by clothes and sunscreens has been widely discussed since then, the photoprotective role of hair cover has only been suggested recently. Green *et al.* (2006) noted that the incidence of CM of the ear was four to seven times higher in men than in women in the Australian and US populations. To test the hypothesis that these data reflected differences in hair coverage, they used experimental manikins and found that hair cover of the ear reduced solar UVB exposure by 81% compared with bare ears (Green *et al.*, 2006). Our clinical results are in accordance with these experimental findings. The "peripheral" area of the head and neck is frequently covered by hair in not only young women but also older ones. In contrast, these areas are less constantly protected in men, particularly as they get older. These differences concerning hair protection could explain the differential distribution of HNM between sexes.

The second major finding of our study is an asymmetrical distribution of HNM according to sex. When studying the laterality in HNM, regardless of their precise location, differences between men and women did not reach significance. When considering only tumors located on the peripheral area, a major difference was observed between both sexes, with nearly three out of four lesions located on the right side in women, contrasting with a large predominance (57.6%) of left-sided tumors in men. A slight left-sided excess of CM has been observed in previous studies in both sexes (Brewster *et al.*, 2007; Bulliard *et al.*, 2008; Dores *et al.*, 2011). Two population-based studies, relying on cancer registries from six countries in three continents and five Swiss regions, respectively (Brewster *et al.*, 2007; Bulliard *et al.*, 2008), demonstrated a left/right ratio of 1.10 to 1.15 in all populations, sexes, age groups, body sites, and categories of Breslow thickness. Recently, Dores *et al.* (2011) confirmed the higher incidence of CM on the left side of the body regardless of the site, but with a larger magnitude in men than in women. They hypothesized that this could be partly because of UV exposure while driving. However, this explanation was considered unsatisfactory because of similar asymmetry at body sites that are not really exposed to UV in cars (Bulliard *et al.*, 2008) and similar findings in countries where the driver's seat is on the right (Australia, England, and Scotland) (Brewster and de Vries, 2008; Bulliard *et al.*, 2008). Apart from chance or confusion in codes for left and right, other hypotheses were a differential side migration of melanocytes from the neural crest to the skin during embryogenesis, and an asymmetry in the circulatory system resulting in differential angiogenesis and response to DNA damage. Although these authors did not specifically study this asymmetry in HNM, literature provides further arguments supporting a role of driving in UV-related skin damage and cutaneous carcinogenesis (Foley *et al.*, 1986, 1993; Singer *et al.*, 1994). In an Australian population of male drivers, Foley *et al.* (1986) observed a correlation between the driving side and both solar keratoses and *in situ* LMMs (most of which were HNMs; Foley *et al.*, 1993). In a retrospective monocentric study of 1,047 skin cancers (82% of which were located on the head and neck), the authors observed a predominance of left-sided cancers, more pronounced in men and for *in situ* melanoma (Butler and Fosko, 2009). Our study including the precise location of HNM definitely confirms and extends these data, showing much larger differences between both sexes than in previous studies, after considering only peripheral lesions.

While traveling in a car, the peripheral area of the head and neck is particularly exposed to UV radiation in an asymmetrical manner depending on the subject's position. UV exposure in a car may vary considerably depending on the type of glass and its thickness, tinting, and/or reflective coating (Moehrle *et al.*, 2003), but UVA rays are able to penetrate glass windows, whereas UVB rays cannot (Butler and Fosko, 2009). Convergent clinical, epidemiological, and experimental data argue for a relationship between UVA and CM (Moan *et al.*, 2012). In France, as very probably in many other countries, the proportion of drivers and the time spent in driving is much higher in men than in women in all age groups. It has been demonstrated that women are more often secondary drivers and drive fewer kilometers than men (Rallu, 1990). Moreover, a significant increase in air conditioning car equipment in France was only observed after 1995 (Bourdeau, 1997), suggesting that before this time, drivers were more likely to drive with open windows and consequently to be exposed to both UVB and UVA radiation. Considering a 10- to 20-year latency period for UV-induced melanocarcinogenesis and the mean age of our population, patients included in this study could belong to generations highly exposed while traveling in a car. Although probably multifactorial when considering the whole body surface, the differential laterality observed according to gender in HNM is undoubtedly consistent with the role of UV exposure in a car.

Although CMs of the peripheral area only account for a minority of HNMs, particularly in women, they occurred in significantly younger patients than those of the central area and could have an important impact in terms of tumor-related morbidity and mortality. Indeed, we found that the peripheral area included a much larger proportion of invasive CMs, a lower proportion of the slow-growing LMM type, and a larger proportion of more rapidly growing types, including nodular CMs, suggesting that this area could include numerous potentially lethal tumors. A recent study found that the location on the scalp or neck (included in the peripheral area according to our definition) was an independent adverse prognostic factor of disease-specific survival in a large series of US patients with HNM (Tseng and Martinez, 2011).

In the absence of individual data, our study was unable to quantify the potential role of hairstyle or sun exposure when traveling in the occurrence of HNM. However, considering a 20% proportion of peripheral melanoma in women as a reference (Table 2), 24 peripheral cases would have been expected in men. Therefore, the observed 68 cases included an excess of 44 peripheral cases, corresponding to 37% of all HNMs in men. As many women also have an insufficient protection by hair, the role of hairstyle and alopecia in the occurrence of HNM could be much higher. Considering both the excess of left-sided peripheral HNMs in men and right-sided peripheral HNMs in women, the excess of lateral HNMs attributable to an asymmetrical sex-related sun exposure could be evaluated at 12% (data not shown). As men can also be exposed in cars as passengers and women as drivers, and frontal exposition in cars may also have a role in the occurrence of HNMs in the central part of the face, the role of sun exposure in cars in the occurrence of HNM could be much higher than suggested by our results.

Overall, these results may have important practical implications. First, the role of hairstyle in CM prevention should not be overlooked. A recent survey of hair professionals demonstrated that they frequently look for suspicious lesions on their customers' scalp, neck, and face and would be receptive to skin cancer education (Bailey *et al.*, 2011). They could thus propose to their customers, especially in at-risk populations, to wear their hair long or to choose a hairstyle covering the peripheral area of their head and neck. Dermatologists, as well as general practitioners, should be aware of the particular vulnerability of male patients, especially those with moderate to severe alopecia. Public health messages could be delivered concerning the importance of reducing UV exposure while in a car to reduce the risk of skin cancer. Car manufacturers should be made aware of the importance of UV protection in their products, with photoprotective windows obtained by tinting or laminating glass or using clear plastic films. Very few people are in the habit of protecting themselves against UV radiation while in a car. Professional drivers should be encouraged to keep windows closed and use air conditioning to reduce occupational UV exposure. The general population should be aware that a car window does not totally protect against sun-related damage and that protection by clothes and sunscreens is still relevant while in a car, especially on sunny days.

## MATERIALS AND METHODS

### Population and inclusion criteria

The study was approved by the Institutional Review Board of Reims University Hospital, Reims, France. The use of human subjects adhered to the Declaration of Helsinki Principles. The patients received an information letter from their referent MD. Patient consent was not required by the local committee of persons' protection. It was based on the population of Champagne-Ardenne, a northeastern region of France, including 1,338,000 inhabitants. The regional melanoma registry OMECHA has been collecting data about all incident *in situ* and invasive CMs in the inhabitants of the region since 2004 (Barbe *et al.*, 2011). It relies on the systematic transmission of pathology reports to the registry by all private and hospital pathology laboratories in the region, as well as those in neighboring parts of the surrounding regions that are liable to diagnose CM in residents of Champagne-Ardenne. Data systematically collected by the registry include: age; sex; patient's area of residence; referent physicians; date of histological diagnosis of CM; anatomic location (head and neck, upper limb excluding the hand and trunk, and lower limb excluding the foot and hand); histological type comprising superficial spreading melanoma, nodular melanoma, LMM, and unclassifiable melanoma; Breslow thickness; and ulceration. CM located in the head and neck area and diagnosed between 1 January 2004 and 31 December 2009 were included in the study.

### Additional data collection

As topographic information available in the registry only mentioned the head and neck location as a single site, additional information regarding anatomic location was collected as follows: (1) all pathology reports were reviewed for more precise information (tumor subsite and laterality); (2) for patients who were followed at Reims University Hospital, medical records from the Departments of Dermatology, Otolaryngology, and Ophthalmology were systematically reviewed; and (3) for patients not followed at Reims University Hospital, a questionnaire regarding precise localization was sent to referent dermatologists and/or general practitioners and surgeons. Those who did not respond were contacted again by telephone up to three times. Location within the head and neck area was separated as follows: scalp, forehead, temple, eyelid, ear, nose, cheek, area around the mouth/chin, and neck. The laterality was recorded as right, left, or median.

### Statistical analysis

Quantitative variables are described as means $\pm$ SD and medians with range and qualitative data as number and percentage. World-standardized incidence rates of HNM were estimated by direct standardization using the distribution by age categories of the world population. These rates were calculated for the entire study period, both in the whole population, including *in situ* and invasive melanomas, and by gender. Univariate comparisons among groups (sex, site, and side) were made using $\chi^2$ test, Fisher's exact test, Student's *t*-test, or Wilcoxon rank test, as appropriate. A multivariate analysis of factors associated with melanoma location was performed using stepwise logistic regressions, with enter and removal limits set at 0.20 and factors significant at $P = 0.20$ included. A *P*-value of $<0.05$ was considered statistically significant. Analyses were performed using SAS version 9.0 (SAS, Cary, NC).

## CONFLICT OF INTEREST

The authors state no conflict of interest.

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